REMARKS

Claim 1 has been amended to add the term "isolated." Support for this amendment can be found at, for example, page 47, lines 26-35. Claims 1-5 are presented for examination. The rejections of the presently pending claims are respectfully traversed.

Priority

The PTO asserts that because the disclosure of PCT/US00/23328 is not enabling for the instant invention, the filing date of the present application is May 2, 2002.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. Applicants submit that for the reasons stated herein, the claimed antibodies are enabled by the disclosure of PCT/US00/23328 and have a credible, substantial, and specific utility. Applicants maintain that the present application is entitled to at least the priority date of August 24, 2000.

Rejection Under 35 U.S.C. §101 – Utility

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Action. The PTO asserts that "[g]iven the increase in message (cDNA) for PRO1013" in normal stomach compared to stomach tumor tissue "one skilled in the art would not assume that a more highly expressed mRNA would directly correlate with increased polypeptide levels." (Office Action at 4-5, emphasis in original). The PTO relies on Haynes *et al.* (1988, Electrophoresis, 19:1862-71), Hu *et al.* (2003, Journal of Proteome Research 2: 405-412), and Chen *et al.* (2002, Molecular and Cellular Proteomics 1:304-313) for the propositions that the literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue, and that polypeptide levels cannot be accurately predicted from mRNA levels. The PTO argues that further research is required to determine the role of PRO1013 in cancer, making the asserted utility not substantial. The PTO also states that declarations submitted with Applicants' previous response are insufficient to overcome the rejection.

Utility – Legal Standard

As previously noted, according to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent

examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., 'question') the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

As previously noted, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a

> whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were

necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly stomach cancer. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1013 polypeptide is expressed at least two-fold higher in normal stomach tissue compared to stomach tumor;

2. Applicants assert that it is well-established in the art that a **change** in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding **change** in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO1013 polypeptide is increased in normal stomach tissue compared to stomach tumor, it is likely that the PRO1013 polypeptide is more highly expressed in normal stomach tissue compared to stomach tumor;

4. Antibodies to proteins which are differentially expressed in certain tumors are useful as diagnostic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that it provides no information regarding differential mRNA expression;

2. The PTO cites Hu *et al.* to support its position that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue;

3. The PTO cites Haynes *et al.* and Chen *et al.* to support its assertion that mRNA levels are not predictive of protein levels;

4. The PTO concludes that based on the cited literature, one of skill in the art would not assume that higher expression of mRNA would correlate with increased polypeptide levels. Therefore, further research needs to be done to determine if the increase or decrease in PRO1013 DNA supports a role for the peptide in cancerous tissue.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, Applicants submit that the Haynes *et al.* Hu *et al.* and Chen *et al.* references are not contrary to Applicants' arguments, and therefore are not evidence to support the PTO's position. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Applicants have established that the Gene Encoding the PRO1013 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO's statement that "the microarray experiments disclosed in the specification (example 18) does measure the level of mRNA expressed in tumor and normal controls." Office Action at 3. Applicants would like to clarify that Example 18 used quantitative PCR analysis of a cDNA library to measure mRNA expression, not a microarray analysis. While the distinction does not matter with respect to the PTO's statement regarding Example 18 and the relevance of the Pennica *et al.* and Sen *et al.* references, Applicants would like to clarify this point for the record.

Applicants next turn to the PTO's arguments based on Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The PTO states that Hu teaches that not all genes with increased expression in cancer have a known or published role in cancer.

As previously noted, in Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published

on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study

means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

In response to similar arguments by Applicants in their previous response, the PTO states that:

> Contrary, to Applicants assertion that Hu et al.'s methodology provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease, the reference teaches that "careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level change". Office Action at 7.

Applicants submit that this does not address the main point of Applicants' previous arguments as elaborated above. Applicants are not relying on any "role" that PRO1013 has in cancer for their asserted utility. Instead, Applicants are relying on the differential expression of PRO1013 in certain tumors compared to their normal tissue counterparts. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

A lack of known role for PRO1013 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1013 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors, and the PTO's response quoted above does not address Applicants' arguments.

In addition, the PTO's own written policies recognize that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state: "the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14); *see also Exhibits 1-3* attached hereto (U.S. Patent Nos. 6,465,185, 6,228,582, and 6,162,604) (patents on

polymorphisms which are indicative of a predisposition to a particular condition are patentable even though they may or may not cause the disease itself). Similarly, here the disclosed nucleic acids, as well as the encoded polypeptides and related antibodies, are useful for determining whether an individual has cancer regardless of whether or not they are the cause of the cancer.

The position of the PTO requiring a known role for PRO1013 in cancer for utility is also inconsistent with the analogous standard for therapeutic utility of a compound where "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis original). Here, the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration previously submitted, establish that there is at least a two-fold difference in PRO1013 cDNA between normal stomach tissue and stomach tumor. Therefore, it follows that expression levels of the PRO1013 gene can be used to distinguish normal stomach tissue from stomach tumor. The PTO has not offered any significant arguments or evidence to the contrary. As Applicants explain below, it is more likely than not that the PRO1013 polypeptide can also be used to distinguish normal stomach tissue from stomach tumor. This provides utility for the claimed antibodies to the PRO1013 polypeptides.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a **change** in the level of mRNA for a particular protein, generally leads to a corresponding **change** in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1013 polypeptide in stomach tumor, it is likely that the PRO1013 polypeptide is differentially expressed; and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO cites Haynes *et al.* (Electrophoresis, 19(11):1862-71 (1998)), Chen *et al.* (Mol. and Cell. Proteomics, 1:304-313 (2002)), and Gygi *et*

al. (Mol. and Cell. Bio., Mar. 1999, 1720-1730) as support for its argument that "the correlation between mRNA expression and protein expression is poor at best." Office Action at 11. For the reasons discussed previously, and reiterated below, Haynes, Chen, and Gygi are not contrary to Applicants' asserted utility.

Haynes studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a **change** in transcript level for a particular gene led to a **change** in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730, previously submitted as Exhibit 6). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *Id.* Thus, it is not clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, and Gygi reports a strong correlation between increasing mRNA levels and increasing protein levels.

The PTO focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result

from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did not say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the same gene leads to a increase or decrease for the corresponding protein. Haynes did not study this issue and says absolutely nothing about it. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's position.

The PTO also cites Chen *et al.* for support for the assertion that polypeptide levels cannot be accurately predicted from mRNA levels. In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples. Like Haynes, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. As discussed above with respect to Haynes, this measurement of a correlation across genes is not relevant to Applicants' asserted utility. Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed antibodies because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for

Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The PTO relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level. This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels are seen, a correlation between mRNA and protein levels was observed. However, if one examines the data points within a small range of mRNA levels for these same genes, e.g. 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range. This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis. Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels vs. protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen

cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis, 18:533-37 (1997)) and Gygi *et al.* (Mol. Cell. Bio., 19:1720-30 (1999)) offer no support for the PTO's position.

Even if the results in Chen supported the PTO's argument, which they do not as discussed above, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. There are other non-transcriptional mechanisms for regulating gene and protein expression (*i.e.*, post-transcriptional regulation of genes, translation efficiency, etc.). However, as shown by the declarations, references, and textbooks discussed below, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between **changes** in mRNA levels and **changes** in protein levels for a particular gene.

In response to Applicants' arguments, the PTO has stated that:

> Contrary, to Applicants assertion that Haynes et al. does not contradict the utility and enablement of the instant claims (page 16 of the response), Haynes et al. states that "These results suggests that even for a population of genes predicted to be relatively homogeneous wit[h] respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA" (page 1863, 2nd paragraph). Although, Applicants assert that there is a strong correlation between mRNA expression Gygi et al. conclude that transcript levels provide little predictive value with respect to the extent of the protein expression (page 1730, last line). Office Action at 6.

Applicants' respectfully submit that these arguments are not responsive to Applicants' main point regarding deficiencies of Haynes and Gygi – both references looked at static levels of mRNA across different genes not changes in the level of expression for a single gene. Therefore, when Haynes and Gygi state that protein levels cannot be accurately predicted from the level of the corresponding mRNA, they are referring only to the static level of mRNA. Applicants have not asserted that protein levels can be predicted from static levels of mRNA, and the asserted utility does not depend on there being a correlation between static levels of mRNA and protein across different genes. Instead, Applicants have asserted that **changes** in mRNA level for an individual gene are generally correlated with **changes** in the level of the encoded protein. Applicants have asserted that because there is a change in the level of mRNA for PRO1013 in stomach tumors compared to their normal tissue counterparts, the level of PRO1013 protein will show a similar change. Predicting the absolute level of protein from the static level of mRNA is not required for this asserted utility since it is the change in the level of mRNA and protein that is important. Haynes and Gygi have absolutely no bearing on this issue since they examined static levels of mRNA for different genes.

According to the Examiner, Orntoft et al. has not provided any information that would correlate the low levels of DNA amplification found in the majority of tested tumors and the associated levels of the encoded proteins. According to the Examiner, Orntoft et al. "could only compare the levels of about 40 well-resolved and focused abundant proteins." Office Action at 7.

Applicants maintain that the fact that the proteins assessed by Orntoft et al. were well-resolved and focused abundant proteins does not impact the observation that only one of the 40 genes analyzed showed disagreement between transcript alteration and protein alteration. Indeed,

the fact that the proteins assessed by Orntoft et al. were well-resolved and focused abundant proteins merely reflects the fact that the methodology which they used to determine protein levels was 2D-PAGE. In such methodology, it is important that one be able to easily distinguish the spot corresponding to a particular protein from adjacent spots resulting from other proteins on the gel and it is also important that one be able to accurately quantitate the amount of the protein being analyzed. Accordingly, such methodology is most readily applied to well-resolved abundant proteins. In view of the foregoing, Applicants maintain that Orntoft et al. supports Applicants' position that, in general, differential expression of mRNA correlates with differential expression of the encoded protein.

Hyman is cited as teaching that even at the level of high amplification and high overexpression, mRNA and protein do not correlate and that, of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. According to the Examiner, this proportion (approximately 2%) does not provide a reasonable expectation that the slight amplification of SEQ ID NO: 22 would be correlated with elevated levels of mRNA. In addition, according to the Examiner, Hyman does not examine protein expression.

Applicants acknowledge that Hyman did not analyze protein expression but looked at the correlation between gene copy number and mRNA levels. Hyman concluded that "the results illustrate a considerable influence of copy number on gene expression patterns." As an initial matter, Applicants remind the PTO that the data in Example 18 reflects mRNA levels rather than the number of copies of the PRO1013 gene in the genome. In view of the foregoing, with respect to the Examiner's concern that approximately 2% of the overexpressed transcripts studied in Hyman were attributable to gene amplification, Applicants maintain that this is immaterial to the utility of the claimed antibodies. The fact that many genes for which the mRNA is overexpressed are overexpressed as a result of a mechanism other than an increase in chromosomal copy number has no bearing on the relationship between mRNA levels and protein levels.

The Examiner also asserts that the Pollack reference does not analyze protein levels, nor does Pollack support the assertion that it is predictable, on the basis of the minimal increase in mRNA levels that the protein would accordingly be found at altered levels. According to the

Examiner, it remains that the significance of the gene amplification data is questionable, and cannot be predictably extrapolated as applying to the claimed protein.

As discussed above, Applicants note that the data in Example 18 reflects mRNA levels rather than the number of copies of the PRO1013 gene in the genome. Furthermore, Applicants maintain that Pollack does not contradict Applicants position that, in general, differential expression of mRNA correlates with differential expression of the encoded protein.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, **including the data discussed in paragraphs 4 and 5 above** [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are

predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (previously submitted as Exhibit 1, herein after Cell 3rd) and (4th ed. 2002) (previously submitted as Exhibit 2, herein after Cell 4th)). Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (previously submitted as Exhibit 3) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming

majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, previously submitted as Exhibit 4. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Zhigang at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Zhigang at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.* at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), previously submitted as Exhibit 5, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. The PTO has not submitted any significant evidence to the contrary.

In response to the second Grimaldi Declaration, the PTO focuses on paragraph 4 of the declaration where he states that chromosomal aberrations which result in aberrant expression of a mRNA and corresponding protein, "the gene product is a promising target for cancer therapy, for

example, by the therapeutic antibody approach." Office Action at 9 (emphasis added). The PTO rejects this argument, stating that unlike Her2/Neu and t(5;14), the PRO1013 gene has not been associated with tumor formation of the development of cancer, and no translocation of the PRO1013 gene is known to occur. The PTO concludes that "in the absence of any of the above information, all the that specification does is present evidence that the mRNA encoding PRO1013 is more highly expressed in an unknown number of samples, and invite the artisan to determine the rest of the story." Office Action at 10.

Applicants submit that the PTO's argument is not responsive to Applicants' previous arguments as reiterated above. Applicants did not rely on paragraph 4 of the second Grimaldi declaration which discusses targets for cancer therapy. Instead, Applicants relied on his statements in paragraph 5 discussing the fact that it is well established that increases or decreases in mRNA generally lead to corresponding increases or decreases in the encoded protein, and that techniques which measure mRNA would have little value and not be so widely used if there were not correlation between the two. The PTO fails to respond to this argument.

In addition, as stated previously, a lack of known role for PRO1013 in cancer does not prevent its use as a diagnostic tool for cancer. The fact that there is no known translocation or mutation of PRO1013, for example, is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1013 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies. (*See, e.g.,* U.S. Patent No. 6,156,500, and U.S. Patent No. 6,562,343 previously submitted as Exhibits 8-9; and U.S. Patent No. 6,414,117, U.S. Patent No. 6,124,433, submitted herewith as Exhibits 4-5.)

Similarly, in response to the Polakis declaration, the PTO states that the specification describes only mRNA expression data, that it is not known whether PRO1013 polypeptide is expressed in normal stomach tissue, and that "[t]here is no nexus between the mRNA expression and PRO1013 polypeptide or antibodies binding PRO1013." The PTO concludes that the disclosure of differential mRNA expression in Example 18 is an invitation to experiment, quoting paragraph 7 of the first Grimaldi declaration "additional studies can then be conducted if further information is desired." Office Action at 10-11.

These arguments are not responsive to Applicants' arguments. While it is true that Example 18 only describes mRNA expression data, there is an obvious nexus between changes in PRO1013 mRNA and the PRO1013 polypeptide and antibody. First, the PRO1013 mRNA encodes the PRO1013 protein. Second, as described in numerous references and declarations above, regulation of mRNA is the primary method for controlling the expression of a gene, and there is a general correlation between changes in mRNA levels and changes in protein levels. Third, the antibody to PRO1013 can be used to detect changes in PRO1013 expression levels. No additional experimentation is needed to establish that it is more likely than not that the claimed antibodies can be used as diagnostic tools for cancer, particularly stomach cancer.

The PTO's reliance on the quote from the first Grimaldi declaration is clearly misplaced when read in context:

> 7. The results of the gene expression studies indicate that the genes of interest can be used to differentiate tumor from normal. The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue. ...**If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor.** Additional studies can then be conducted if further information is desired. (emphasis added)

It is obvious that Mr. Grimaldi was stating that it is his expert opinion that the information provided in Example 18 is sufficient to use the gene, protein and antibody as diagnostic tools, and that no further testing or information is required. However, if additional information is desired, such as the role of the gene or protein in cancer formation or growth, additional studies can be conducted. It is disingenuous of the PTO to take this quote out of context to suggest that

Mr. Grimaldi is stating that further research is required to use the claimed invention when the remainder of his declaration is clearly stating otherwise.

Finally, Applicants turn to the PTO's discussion of the Applicants' supporting references. The PTO acknowledges the submission of two Alberts references, as well as the Lewin, Zhigang, and Meric references. *See* Office Action at 11. However, the PTO only responds to the Meric reference, essentially ignoring the remaining references. The PTO states that Meric teaches that gene expression is complicated, and regulated at numerous levels, and that changes in mRNA sequences increase or decrease translation efficiency. Office Action at 13.

These arguments are not responsive. Applicants have already acknowledged that gene expression is regulated at numerous levels. However, as the supporting references and declarations Applicants have supplied make clear, regulation of mRNA levels is the predominant mechanism of control for the majority of genes. Meric supports this assertion because "[t]he **fundamental principle** of molecular therapeutics in cancer is to exploit the **differences** in gene expression between cancer cells and normal cells." Meric *et al.* at 971 (emphasis added). The only reason mRNA is of any interest in studying the mechanism of cancer formation and growth is because mRNA encodes protein. If there were no general correlation between differences in mRNA and differences in protein, there would be no reason to study changes in mRNA.

In summary, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1013 mRNA is more highly expressed in normal stomach tissue compared to stomach tumor, the PRO1013 polypeptide will also be more highly expressed in normal stomach tissue compared to stomach tumor. This differential expression of the PRO1013 polypeptide makes antibodies to it useful as diagnostic tools for cancer.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In*

re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**." M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

The PTO has failed to offer any arguments or cite any references to establish "that one of ordinary skill in the art would reasonably doubt" that antibodies to a polypeptide differentially expressed in certain tumors can be used as a diagnostic tool. Hu *et al.*, Haynes *et al.*, Gygi *et al.*, and Chen *et al.* do not support the PTO's position and are not contrary to Applicants' asserted utility. Likewise, the PTO has not offered any substantial arguments or evidence to rebut the

numerous declarations and references Applicants' have submitted in support of their asserted utility. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly rectal and kidney cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO1013. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1013 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene for the PRO1013 polypeptide is expressed at least two-fold higher in normal stomach tissue compared to stomach tumor. These data are strong evidence that the PRO1013 gene and polypeptide are associated with stomach tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1013 gene and polypeptide with a specific disease. The asserted utility for antibodies to the PRO1013 polypeptide as a diagnostic tool for cancer, particularly stomach tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has asserted three arguments to support its conclusion that based on the cited literature, one of skill in the art would not assume that higher expression of mRNA would correlate with increased polypeptide levels: (1) the PTO has challenged the reliability of the

evidence reported in Example 18; (2) PTO cites Hu *et al.* to support its position that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue; and (3) the PTO cites Haynes *et al.*, Gygi *et al.*, and Chen *et al.* to support its assertion that mRNA levels are not predictive of protein levels. The PTO states that further research needs to be done to determine if the increase or decrease in PRO1013 DNA supports a role for the peptide in cancerous tissue. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the gene expression data in Example 18 are real and significant. This declaration also indicates that given the relative difference of at least two-fold in expression levels, the disclosed nucleic acids and corresponding polypeptides and antibodies have utility as cancer diagnostic tools. Hu *et al.* does not support the PTO's position, and is not contrary to Applicants' asserted utility. Thus, the PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in protein levels. Haynes *et al.* and Gygi *et al.* do not address this issue, and are not contrary to Applicants' asserted utility. Portions of Chen support Applicants' position, while the remainder is not contrary to Applicants' assertion that generally there is a correlation. Thus, the PTO has not offered any substantial reason or evidence to question Applicants' declarations and supporting references.

Third, Applicants have shown that it is not necessary to know what role PRO1013 plays in cancer to use it as a diagnostic tool. The PTO's own guidelines recognize this fact, and numerous patents have issued which claim differentially expressed polypeptides and antibodies to the same, or methods employing such antibodies.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO1013 gene and polypeptide are differentially expressed in certain cancer cells compared to

the corresponding normal cells. This is not a general utility that would apply to the broad class of antibodies.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO1013 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also rejects Claims 1-5 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Conclusion

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Aug. 19, 2005

By: _____

Daniel Hart
Registration No. 40,637
Attorney of Record
Customer No. 30,313
(619) 235-8550

1876956
081805